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# Antipropulsive effects of central and peripheral morphine in the rat gastrointestinal tract

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The antipropulsive effects of centrally or peripherally administered morphine have been examined at three levels of the rat gastrointestinal tract. Adult male rats were anaesthetized with pentobarbitone (50 mg $kg^{-1}$ i.p.) and were implanted with an intraluminal catheter in either the proximal duodenum or mid-jejunum. Other animals were also implanted with a cannula in the right lateral cerebral ventricle. Gastric emptying and transit were determined selectively by measuring the progression of a radioactive chromium (CR-51) solution, given intragastrically for tests of gastric emptying or instilled into the proximal or distal intestinal catheter for determination of intestinal transit, 30 min after administration of morphine or saline given either subcutaneously (s.c.) or intracerebroventricularly (i.c.v.). Morphine given either s.c. (5 mg $kg^{-1}$) or i.c.v. (30 μg, total dose) significantly inhibited gastric emptying and transit through bulk portions of the small intestine indicating that by either route it inhibits propulsion at all three levels of the gastrointestinal tract.

Morphine inhibits gastrointestinal propulsion in the rat when administered either centrally or peripherally (Parolaro et al 1977; Stewart et al 1978; Schulz et al 1979; Galligan & Burks 1982). Subcutaneously or intracerebroventricularly administered morphine reduces the caudal progression of a test meal delivered intragastrically or intraduodenally, indicating inhibition of stomach emptying and proximal intestinal transit. The purpose of this report was to compare the relative inhibitory effectiveness of centrally or peripherally administered morphine on the progression of a test meal delivered either into the rat stomach, proximal small intestine or distal small intestine.

## *Methods*

Adult male rats (Sprague Dawley, USA) (200–500 g) were anaesthetized with sodium pentobarbitone (50 mg $kg^{-1}$ i.p.) and implanted with an indwelling catheter in either the proximal duodenum, 3 cm distal to the gastroduodenal junction, or at the approximate midpoint of the small intestine, 50 cm proximal to the caecum, by the method of Stewart et al (1978). The free end of the catheter was exteriorized and was protected by a shoulder harness made from paper tape. In order to administer substances intracerebroventricularly (i.c.v.), a number of animals were additionally implanted with a polyethylene cannula (PE 10) in the right lateral cerebral ventricle (Robinson et al 1969; de Balbian Verster et al 1971). Animals used to study the effects of morphine on gastric emptying did not require gastrointestinal catheter placement, and were only implanted with an intracerebroventricular cannula if necessary.

All animals were housed singly in cages with wire mesh bottoms. Experiments were performed on the unanaesthetized animals 6–10 days after surgical preparation. Animals used for intestinal transit studies were fasted for 18 h before experimentation. Animals used for gastric emptying studies were fasted for 48 h before experimentation but were provided with two small sugar blocks at 24 h. Water was freely available to all animals.

Animals were given morphine sulphate, or 0·9% NaCl, either subcutaneously (s.c.) or i.c.v. 30 min before testing, at a dose of 5 mg $kg^{-1}$ s.c. or 30 μg (total dose) i.c.v. calculated as the salt. All injections made s.c. were in a volume of 1 ml $kg^{-1}$ while injections made i.c.v. were in a volume of 10 μl.

Effects of morphine or saline on gastric emptying were determined by administering a 1·0 ml solution of isotonic radioactive sodium chromate (51-Cr, 0·5 μCi) by gavage. Animals were killed by cervical dislocation 10 min after chromium administration. After metal clamps had been placed at the lower oesophageal and gastroduodenal junctions, the stomach was carefully removed and consecutively placed in counting vials. The resulting γ emissions, counted for 1 min, were used to determined the percentage of solution remaining in the stomach.

Drug effects on transit through the proximal or distal portion of the small intestine were determined similarly. The radioactive chromium solution (0·2 ml, 0·5 μCi) was instilled either into the proximal or distal intestinal catheter. The animals were killed by cervical dislocation 10 min after marker instillation and either the proximal or distal 50 cm of the small intestine was carefully removed. Each intestinal portion was divided into 10 equal segments and the number of radioactive counts were determined for each. The γ emission data were used to compute the maximal percentage of proximal or distal intestine traversed by marker using mathematical methods as described by Stewart et al (1978). Resulting data were analysed using a Student's *t*-test. Values of $P < 0.05$ were considered significantly different.

## *Results and discussion*

A significantly greater percentage ($P < 0.05$) of chromium remained in the stomach after morphine (5 mg $kg^{-1}$) s.c. than after saline (1 ml $kg^{-1}$) s.c. (Table

* Correspondence.

Table 1. Effects of morphine given s.c. (5 mg kg$^{-1}$) or i.c.v. (30 μg total dose) on gastric emptying and on propulsion through the proximal and distal small intestine.

| | A. Gastric emptying | | B. Proximal small intestine | | C. Distal small intestine | |
|---|---|---|---|---|---|---|
| | s.c. | i.c.v. | s.c. | i.c.v. | s.c. | i.c.v. |
| | % Remaining[a] | % Remaining | % Transit | % Transit | % Transit | % Transit |
| Saline | 60·1 ± 4·74 (9)[b] | 38·5 ± 4·20 (10) | 89·9 ± 7·48 (6) | 91·3 ± 10·99 (6) | 59·2 ± 3·80 (6) | 51·4 ± 5·54 (6) |
| Morphine | 74·1 ± 2·19 (9)*[c] | 66·7 ± 6·75 (6)** | 56·1 ± 5·06 (6)** | 49·9 ± 5·98 (6)** | 33·0 ± 1·59 (6)** | 31·3 ± 2·86 (6)** |
| Water | — | 41·2 ± 5·74 (6) | — | — | — | — |

[a] Percentage (mean ± s.e.m.) of Cr solution remaining in the stomach after 10 min.
[b] Numbers in parentheses indicate number of animals.
[c] *$P < 0.05$; **$P < 0.01$ by a Student's $t$-test.
[d] Percentage (mean ± s.e.m.) of the proximal or distal 50 cm of small intestine traversed by Cr solution in 10 min.

1A). Similarly, morphine given i.c.v. (30 μg, total dose) also inhibited ($P < 0.01$) the emptying of chromium from the stomach when compared with saline (10 μl) given i.c.v. (Table 1A). The effects of s.c. and i.c.v. morphine appeared to differ quantitatively. Morphine given s.c. raised by 14% the amount of chromium remaining in the stomach compared with control saline, whereas morphine given i.c.v. raised the percentage of chromium remaining in the stomach by 28·2% compared with the control. The greater effectiveness of centrally administered morphine in inhibiting stomach emptying may be more apparent than real. Animals injected i.c.v. with saline (10 μl) emptied chromium from the stomach relatively rapidly when compared with saline given s.c. Thus morphine was acting in a setting of rapid gastric emptying in the studies of central morphine. The source of enhanced stomach emptying after centrally administered saline was not determined; however, relatively rapid stomach emptying also occurred after distilled water (10 μl) given i.c.v. (Table 1A). This suggests that the effects of i.c.v. saline did not result from centrally administered sodium or chloride ion, but may have resulted from some aspect of the central administration technique. The results confirm previous reports that morphine inhibits stomach emptying when administered either centrally or peripherally (Galligan & Burks 1982).

Morphine given s.c. and i.c.v. also inhibited ($P < 0.01$) the percentage of the proximal and distal portions of the small intestine traversed by chromium during the experimental period when compared with saline control values (Table 1B, C). The inhibition of transit was slightly greater quantitatively in the proximal small intestine than in the distal small intestine, again perhaps the result of greater baseline marker progression in the proximal bowel than in the distal bowel. Greater progression of marker might be expected in the proximal portions of the small intestine than in the distal small intestine because of the aborally decreasing gradient of contractile activity found along the rat small intestine (Ruckebusch & Fioramonti 1975: Weisbrodt et al 1980). Morphine may inhibit small intestinal propulsion either by inhibiting intestinal smooth muscle contractions (Weisbrodt et al 1980), or by increasing intestinal water and electrolyte absorption (Lee & Couper 1980).

We conclude that morphine given s.c. or in a relatively small total dose i.c.v. inhibits gastric emptying and propulsion through both the proximal and distal small intestine of the rat.

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